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Welcome to Yale Cancer Answers with your host doctor Anees Chagpar. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, it’s a conversation about Cancer Research and COVID-19 with Doctor Akiko Iwasaki. Doctor Iwasaki is the Waldemar Von Zedtwitz Professor of Immunobiology and Molecular, Cellular and Developmental Biology at the Yale School of Medicine where doctor Chagpar is a professor of surgical oncology.

Akiko, I know you from all of your work in cancer, but maybe we can take a step back and you can tell us a little bit more about yourself and your background.

Sure, I am an immunologist. My love has been studying how immune responses are generated against different viruses. So over the years we’ve learned...
a lot about the immune system through studying infection with a variety of viruses, including herpes virus, influenza virus, rhinovirus, and many others. So what we've been able to do is leverage this understanding of antiviral immunity to apply it to cancer. For example, we've been understanding how T cells are activated against viruses and how they migrate throughout the body to fight against viral infection and we leverage this understanding to apply it to a local tumor environment where we can trigger T cells to be recruited to a particular site, in this case a tumor to be able to attack the tumor cells better. And that really sounds a lot like immunotherapy, which has been such a huge advance, it is a form of immunotherapy. So this strategy that I'm describing is called Prime and pull. A prime describes the fact that we are priming T cell response against a specific antigen, so in this case we are
targeting tumor antigens.

And pull refers to the fact that we are eliciting TCL recruitment to the site using chemo coins, so this is a two step vaccination strategy to target the immune cells to the site of tumor growth and it’s a little bit more specific than a checkpoint inhibitor therapy, where we’re kind of taking out the brake from all T cells.

But in our case we are targeting specific antigens that the tumors expressed with a targeted prime and pull approach, how do the viruses play into that prime and pull approach? Right, we are targeting viral induced tumors such as human papilloma virus induced cervical tumors, and essentially what we’re doing is to stimulate T cells against the virus antigens with the prime and pulling them into the site.

In this case, the cervix, using chemokine or a chemokine inducing agent, so that’s where the virus comes in. Viruses actually cause many different types of tumors, including cervical cancer, and we’re kind of using virus as a tag...
to be able to stimulate the specific T cell immunity against those tumor cells. That’s kind of interesting. You take these T cells and you prime them to this virus so that you can kind of attack the cancer. But recently your research has kind of shifted now that we’re all thinking about another virus, being COVID-19, so tell us how that pivot happened. When the news about COVID-19 started to emerge, we quickly reorganize the laboratory so that we can all focus on the COVID-19 research. So I remember having a lab meeting asking the lab members if anybody’s interested in working on COVID-19 and to help with the COVID-19 testing throughout the community. And virtually everybody stepped up to the challenge. So essentially everyone you know just sort of one day stop doing their other research to focus on COVID-19 very quickly. And you were previously studying things like cancer related viruses, HPV and so on. How is COVID-19 similar versus different? And how could you focus on another virus?
The advantage of what we’ve been doing is that we weren’t focusing on any particular virus. So as I mentioned, we’ve been studying genital herpes influenza virus causing the flu symptoms, rhinoviruses in the nose, and so we were pretty versatile to begin with, so we were able to quickly focus on COVID-19 because of our expertise in the respiratory virus infection, and it wasn’t that much of a leap for us to pivot to COVID-19.

Is COVID-19 like every other virus, though? Many of us have experienced rhinovirus, the virus that gives us the common cold, but it doesn’t have the impact that COVID-19 has had, so in terms of the virus itself, are they different? Oh yes, every virus is very different in its unique way of evading the immune system and to transmit from one host to another. And so even though we were studying other respiratory viruses, COVID-19 is by far the most severe
and contagious virus
we have shifted to studying and part of it has to do with the fact that none of us had any pre existing immunity to this virus. I would imagine that when this pandemic hit and many researchers like yourself and people in your lab started to try to figure out in a very rapid fashion what was going on with this virus, I mean, the fact that you were actually studying immunity in terms of viruses and how you could get your immune system to attack seems to be really relevant because as we try to figure out how can people resist this virus, which is completely novel to all of our immune systems and potentially develop a vaccine, that is really interesting. Tell us a little bit more about what you did in your lab to move that research forward. Yeah, so as you say, we were very fortunate to be in a position we were because of our previous experience as well as understanding in general about antiviral immunity to be able to quickly tackle some of the key aspects of COVID-19.
So for instance we are studying in real time in response to COVID-19 from patients that enroll in our study and trying to figure out what type of immune responses confer protection in recovery versus which of those responses lead to wars, disease outcome, and even to death. So we were able to mobilize the team to be able to look at these issues and the fact that we were able to do this also has to do with collaborators, we have a large network of collaborators who are recruiting patients into the study who are collecting samples, archiving samples, analyzing clinical data sets, and just a whole variety of tasks that are needed to happen in order for us to study our response to COVID-19. So we’re very fortunate to be in a place where we can do this. And what have you found so far? We’re finding, as I mentioned in real time, some patients that come in the hospital do well and they recover and they get discharged. And others go on to develop worst disease and what we’re finding is that the immune response during
the first 10 to 12 days of symptom onset can really inform us about how they might do in the future. So it's almost like we can predict the disease trajectory of patients based on the very early immune signatures that we're detecting from patients. That seems to make sense because we know that people who are immunodeficient or immuno compromised tend to have more severe illness with COVID-19. But aside from not having an immunodeficiency, do we know in normal people? I mean we've heard on the news people who are otherwise perfectly healthy succumbing to COVID-19. Do we know what it is about their immune system that puts them more at risk and perhaps more importantly, do we know what we can do to ramp up people's immune systems to potentially give them a boost or a test to make sure that their immune system is strong enough to fight this virus? I think we're getting there. I would say we're not there yet, but we are understanding a lot at least with respect to the immune response,
how patients are responding to this virus and what that does to viral clearance versus disease such as cytokine storm. And to get back to your question about some people who are otherwise very healthy or have gotten COVID-19 and did very poorly with this disease, part of it has to do with the viral exposure. If you’re being exposed to a large dose of virus, and if you’re inhaling that virus into the deep respiratory area, then that might cause a different type of disease than if you were getting just a few viral particles up your nose and they’re just sort of remaining in the upper respiratory tract, and so one has to do with the viral exposure in the dose, and the other has to do with what I was talking about the person’s propensity to develop different types of immune response. So for instance, though people who are doing well with this disease appear to focus their response in tissue repair mechanisms, so people who can secrete growth factors to repair the damage in the lung are doing better, while those people who are initiating more of the cytokine storm type of response,
even early during the infection

tend to do worse,

so I think a lot has to do

with viral dose exposure.

The route of exposure as well

as the propensity of developing

different types of immune responses.

Tell us a little bit more about this

cytokine storm response. What is that exactly?

You often hear about the cytokine storm.

It’s essentially what happens when

the immune system is triggered by the

virus infection in a matter without

having any brakes.

So usually what happens during

that the viruses meet rigorous

cytokine response,

but quickly the innate and adaptive

immune response contains that virus.

So that the response is

tapered down within

a few days,

whereas in this case of COVID-19,

some patients are having this very

prolonged and uncontrolled cytokine release.

And when that happens the cytokines

themselves could have toxic impact

on delicate tissues such as the

lung and the microvasculature

that are surrounding the Alveolae.
So it’s really having a negative impact rather than trying to contain the virus and so one of the key hallmarks of disease progression appears to be having these kind of cytokine storms even during early infection. So it will be important to understand which people have which kind of response so that we can kind of predict how people will do to COVID-19. We’re going to learn more about that right after we take a short break for a medical minute. Please stay tuned to learn more about COVID-19 and cancer with my guest doctor Akiko Iwasaki. Support for Yale Cancer Answers comes from AstraZeneca, working to change how cancer is treated with personalized medicine. Learn more at astrazeneca-us.com. This is a medical minute about colorectal cancer. When detected early, colorectal cancer is easily treated and highly curable and as a result, it’s recommended that men and women over the age of 50 have regular colonoscopies to screen for the disease. Tumor gene analysis has helped improve management of colorectal
cancer by identifying the patients most likely to benefit from chemotherapy and newer targeted agents, resulting in more patient-specific treatments. More information is available at yalecancercenter.org.

You're listening to Connecticut public radio. Welcome back to Yale Cancer Answers. This is doctor in East shag part and I'm joined tonight by my guest Doctor Akiko Iwasaki. We're talking about her research looking into COVID-19 an right before the break. Akiko, you were talking about how one of the things you mentioned was that there was a difference between people who mounted an immune response that was really localized where they had an ability to repair tissues versus people whose immune response was this quote cytokine storm kind where their immune system went crazy and started attacking all kinds of things and those people did less well. So my question to you is, do we know
which kind of people are which?
Am I going to be the kind of person who is going to have a localized response, or whether my immune system will go crazy. Are there factors that predict that? Either my medical history if I have autoimmune conditions, for example, race, gender, age? What goes into that? Do we know? We’re starting to find out that there are certain factors. a host of factors that affect how people respond in a matter of protective versus non protective and harmful and one of the factors that we’re finding is that women tend to do better with COVID-19 disease than men and this has been reported throughout the world and we are honing in on why that is. Why sex makes a difference in our ability to fight off this infection, and one of the things coming out from this study, which is supported by Women’s Health research at Yale, is the fact that women make better T cell response, while men tend to make these cytokine storm type of response, especially as they age. That’s really interesting.
Do we know why that is?

I mean, does that have something to do with estrogen versus testosterone?

Mind you, we would expect that as women age, their estrogen levels go down, so what might be the underlying mechanism of that?

That’s a great question.

We don’t know whether sex hormones like testosterone or estrogen can be the only answer to this question.

And especially as you say we’re looking at patients in the age group of 70s, eighties, 90s.

These sex hormones may not be playing a big role and so the molecular underpinning of why women do better is still unclear.

But what we do know is that if you plot age and T cell response in the different sex groups, women tend to age better in terms of T cell immunity that even older women are able to mount a pretty robust response during this COVID-19 infection.

Whereas men who age in the older group tend to really be poor inducers of T cell response and that correlates with...
their poor prognosis in the future, so it really is painting a picture that women tend to age better with the immune response. I wonder too, there are certain autoimmune conditions, so things like Hashimoto’s thyroiditis for example where your immune system attacks your thyroid that are more prevalent in women versus men. So is it that women have a stronger immune system? Or is it that their immune system just tends to be better regulated against COVID-19 because men have more likely this cytokine storm condition. Yes, so it is true that many autoimmune diseases have female prevalence, and it’s also true that for other viruses women do tend to make better immune response. Even for flu vaccines, it’s been shown that women mount a better antibody response to vaccines, so it may be that women, because of their capacity to mount a better immune response, they’re doing better with this COVID-19 disease, whereas men,
especially as they age, they fail to mount a very good adaptive immune response, and therefore they are secreting more cytokine because of their inability to kill the infected cells and control the virus.

Do we know for women, what are predisposing factors that make women do worse? So are there other factors than gender that may play a role or that may interact that would predispose one woman to do well versus some women to do poorly? That’s a really good question. We don’t really know what other factors influence how women tend to do worse with this disease. One of the things that we obtained from this particular study is that women who tend to make cytokine response, one like the cytokine storm type of response do worse with this disease. So even if they are able to mount a robust immunity if there are also triggering the cytokine response then they tend to do poorly, so it’s really a balance between their ability to...
regulate the cytokine response at the same time as mounting a robust T cell response that tend to dictate their disease trajectory, but we don’t know aside from gender, what really causes people. Some people to have more of a cytokine storm response. Is not. Right, so the one thing other than the age, which is a very clear sort of disease risk factor. The other thing that came out of this study is the BMI. Especially man who tended to do worse with this disease had higher BMI. So yeah, obesity is contributing to disease progression, especially in men, not so much in women. So what makes women suffer from worst disease outcome? It is still unclear. And so in men, is it that their BMI actually changes their immune response such that higher BMI is associated with more of this cytokine storm? Or is it working through another independent pathway? Yeah, another really great question. That’s something that we are planning to look at more carefully.
So our first study is currently posted and we’ve done this first analysis. But there are a lot of questions including the BMI question and the other including whether a sex hormone or other parameters are associated. Women can explain some of the features that we’re seeing. And I guess the other question that I have is sadly we can’t do much about the gender that we’re born with, but in terms of people who are transgendered, people that have changed their gender, what happens to their immunity and therefore their risk in terms of COVID-19? Another really great question. Unfortunately, because of the number of patients recruited being rather limited, it’s less than 100 patients, we didn’t have enough to dissect what happens to transgendered people in our cohort, but that’s something we would love to get into in the future, especially once we understand better the
molecular basis for the differences in sex. we can actually attract those molecules to see what happens in transgender settings and whether that would dictate their ability to mount a protective immunity or a more harmful immune response. Yeah, I mean I think it’s going to tie in as well to your studies. Looking at hormones, and certainly people who have to take exogeneous hormones as they are transitioning that may certainly play a role and then I guess the other question is OK, let’s suppose that you have whatever immunity you have, and let’s suppose that you there is a way to know for example, could you take a blood specimen from me and tell me, you’re more likely to have a cytokine storm reaction versus you’re more likely to have an adaptive response. I mean, is there a way to tell that just in people in general? Yeah, so that would be the
next step.
Right now we’re focusing on infected people to try to understand these seeming differences, but ultimately what we want to do is to be able to predict before the infection whether a person might do better or worse from this disease and what we can do to intervene with the disease process. So another element that we’re looking into is the genetics. Are there genetic differences between people who do worse versus those who recover from this disease? Even accounting for all the other parameters we discussed, such as aging and BMI or their genetic differences that we can look into and that may be able to play into this prediction of whether a person might do worse or better with this disease. Have you found any racial differences that might give you a glimmer into genetics? Those types of studies really require thousands of agents, and currently this particular study is focused on a handful.
about 100 patients, and so the genetic studies that’s ongoing at Yale are really in recruiting thousands of patients to be able to look at these issues and so I’m hopeful that those answers will be forthcoming. I realize that probably the next step is how exactly do you intervene? I mean, because regardless of whether you could tell me that I’m more likely to have a cytokine storm response, or I’m more likely to have an adaptive response, are there ways that we can intervene that would help us to have a better immune response, whether to COVID-19 or anything else whether that intervention is a drug or some sort of intervention like that or whether it would be something like a particular dietary a particular dietary intervention or getting more exercise, which seems to be the cure all for everything these days and certainly would help with the BMI, at least in men, do we have a sense
either from your current work or from your previous work of what things might actually be helpful in terms of changing, or even is it possible to change people’s innate immune response from one that is a cytokine storm to being a more adaptive immune response. Yes, there are ways to intervene. For instance, I mentioned that men who developed cell immunity tend to do worse from COVID-19. What this tells us is that we should be enhancing their T cell response in order for older men to fight this disease better. So a vaccine that might stimulate good T cell response might be a way to at least prevent future infection and disease in older men, and similarly women who have these cytokine storms tend to do worse even if they had good T cell immunity. So this means that interventions such as monoclonal antibodies to block cytokines might be a good option for women who already exhibit early levels of these cytokines, and getting back to other interventions, non-hospital interventions, obviously getting exercise and getting enough sleep and reducing
stress is in general very helpful, but we’ve also done a study where we fed animals ketogenic diets and ketogenic diets protected these mice from disease that happened after influenza infection and what the impact it had was interesting because it increased these innate like lymphocytes, the Gamma Delta T cells in the lung and they were better able to fight off influenza infection, so there may be a dietary way of preventing severe diseases from respiratory infections.

If you have questions the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at Yalecancercenter.org. We hope you’ll join us next week to learn more about the fight against cancer here on Connecticut public radio.